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Influence of Reversible Segmental Left Ventricular Dysfunction on Heart Period Variability in Patients With One-Vessel Coronary Artery Disease

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Objectives. **This study evaluated the relation between reversible segmental left ventricular dysfunction and frequency domain measures of heart period variability in patients with coronary artery disease.**

Background. **Heart period variability is frequently reduced in patients with coronary artery disease. However, the mechanisms of this reduction are still unclear.**

Methods. **Echocardiographic left ventricular wall motion and frequency domain measures of heart period variability were evaluated in 32 patients with one-vessel coronary artery disease before and 16 to 24 days after successful percutaneous transluminal coronary angioplasty. Of these, 12 patients (Group A) had normal and 20 patients (Group B) had abnormal regional wall motion. A control group of 15 healthy subjects (Group C) underwent 24-h Holter recording twice at 2-week intervals to check for spontaneous variations.**

Results. **At baseline, low and high frequency power were lower in Group B than in Groups A and C, whereas no difference was detectable in ultra low and very low frequency and total power. After coronary angioplasty, regional wall motion and frequency domain measures of heart period variability were unchanged in Group A. In Group B the mean (±SD) summed segment score improved from 17.1 ± 3.6 to 12.8 ± 2.0 ($p < 0.01$), and mean low and high frequency power (logarithmic units) increased from 6.14 ± 0.23 to 6.35 ± 0.34 ($p < 0.01$) and from 5.43 ± 0.32 to 5.68 ± 0.52 ($p < 0.01$), respectively. Furthermore, low and high frequency power, lower at baseline in Group B than in the other two groups, were comparable in the three groups after coronary angioplasty.**

Conclusions. **This study demonstrates that segmental left ventricular dysfunction is involved in determining sympathovagal imbalance in patients with one-vessel coronary artery disease; the reversal of left ventricular dysfunction by successful coronary angioplasty improves the heart period power spectrum. Thus, alterations in cardiac geometry influence the discharge of afferent sympathetic mechanoreceptors, contributing to the derangement in autonomic control of heart rate.**

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It is well known that myocardial ischemia can trigger cardiac reflexes as a consequence of activation of sensory endings located in the left ventricle (1–4). Sympathovagal imbalance has been described after acute myocardial infarction using different methods (5–8) and is currently used to identify patients at high risk of subsequent events (9–11).

Furthermore, a dynamic withdrawal of vagal tone has been reported during periods of asymptomatic ST segment depression and has been hypothesized to contribute to the development of ischemic ventricular arrhythmias (12). Imbalance in autonomic control of heart rate has also been reported in patients with chronic myocardial hypoperfusion (13–15); however, the mechanism of this association is still unclear.

In this study we evaluated the relation between segmental left ventricular dysfunction and sympathovagal imbalance. For this purpose we assessed frequency domain measures of heart period variability in patients with one-vessel coronary artery disease with and without regional left ventricular dysfunction. Furthermore, we evaluated the effects of successful percutaneous transluminal coronary angioplasty on heart period variability in these two subsets of patients.

Methods

Patients. We considered 40 consecutive patients (36 men, 4 women; mean [±SD] age 56.9 ± 8.4 years) with one-vessel coronary artery disease who underwent successful coronary angioplasty between November 1992 and May 1993; three patients with a failed attempt at coronary angioplasty in the same period were excluded.

Patients with a history of 1) myocardial infarction that

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Table 1. Clinical Characteristics of Patients With Normal Segmental Left Ventricular Wall Motion (Group A) Undergoing Coronary Angioplasty

Pt No.	Age (yr)/ Gender	Previous Infarct Location	EF (%)	Indication for PTCA	Vessel Dilated	Stenosis Severity Before PTCA (%)	Summed Score Before PTCA	Summed Score After PTCA
Previous MI								
1	65/M	IWMI	50	Stable angina	LCx	75	11	11
2	57/M	NQWMI	52	Stable angina	LAD	75	11	11
3	64/M	IWMI	48	Stable angina	LCx	75	11	11
4	49/M	NQWMI	55	Stable angina	LCx	75	11	11
No previous MI								
5	58/M		51	Unstable angina	LAD	90	11	11
6	61/M		49	Unstable angina	LAD	80	11	11
7	56/M		57	Unstable angina	LAD	80	11	11
8	61/M		62	Stable angina	RCA	90	11	11
9	49/M		51	Unstable angina	LAD	90	11	11
10	64/M		53	Stable angina	LAD	80	11	11
11	51/M		57	Silent ischemia	LAD	80	11	11
12	50/F		59	Stable angina	RCA	90	11	11

EF = ejection fraction; F = female; IWMI = inferior wall myocardial infarction (MI); LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = male; NQWMI = non-Q wave myocardial infarction; Pt = patient; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

occurred within 1 year, 2) hypertension, 3) diabetes; patients with clinical signs of congestive heart failure; and patients with technically poor or uninterpretable echocardiograms were excluded from the study. Of the 40 patients enrolled, 15 had normal echocardiographic wall motion (Group A), and 25 had segmental left ventricular dysfunction (Group B).

The characteristics of the enrolled patients are reported in Tables 1 and 2. *Unstable angina* was defined as recent episodes of angina at rest, and all patients were in clinical class IIB or IIIB according to the Braunwald classification (16), without enzymatic evidence of ongoing myocardial infarction. *Stable angina* was defined as exertional chest

Table 2. Clinical Characteristics of Patients With Abnormal Segmental Left Ventricular Wall Motion (Group B) Undergoing Coronary Angioplasty

Pt No.	Age (yr)/ Gender	Previous Infarct Location	EF (%)	Indication for PTCA	Vessel Dilated	Stenosis Severity Before PTCA (%)	Summed Score Before PTCA	Summed Score After PTCA
Previous MI								
1	65/M	AWMI	47	Stable angina	LAD	80	17	12
2	57/M	AWMI	38	Unstable angina	LAD	90	19	17
3	64/M	AWMI	35	Stable angina	LAD	80	27	12
4	49/M	AWMI	42	Silent ischemia	LAD	90	15	12
5	64/F	AWMI	36	Stable angina	LAD	90	21	17
6	51/M	IWMI	48	Stable angina	RCA	99	15	13
7	50/M	NQWMI	50	Silent ischemia	LCx	95	14	11
8	40/M	AWMI	48	Unstable angina	LAD	80	15	13
9	66/M	AWMI	37	Stable angina	LAD	80	19	17
10	56/M	AWMI	46	Unstable angina	LAD	90	15	12
11	64/M	AWMI	38	Stable angina	LAD	80	24	13
12	40/M	AWMI	46	Stable angina	LAD	85	18	13
No previous MI								
13	58/M		51	Unstable angina	LAD	85	17	11
14	61/M		49	Unstable angina	LAD	95	14	11
15	56/M		41	Unstable angina	LAD	85	18	14
16	61/M		53	Unstable angina	LAD	95	14	11
17	49/M		50	Silent ischemia	LAD	90	15	12
18	64/F		47	Stable angina	LAD	90	17	11
19	51/M		47	Stable angina	RCA	90	15	13
20	50/M		51	Stable angina	LCx	95	13	11

AWMI = anterior wall myocardial infarction (MI); other abbreviations as in Table 1.

discomfort relieved by rest or administration of nitrates, without recent change in frequency, duration or stimulus required to precipitate symptoms. *Silent ischemia* was defined by the presence of ischemic ST segment changes without angina symptoms at either 24-h Holter recording or exercise stress test.

Each patient signed a written informed consent form approved by the Ethical Committee of our institution.

Study protocol. Holter monitoring for heart period variability analysis and two-dimensional echocardiography were performed in hospital 24 to 48 h before coronary angioplasty and were repeated in the outpatient setting between 16 and 24 days after angioplasty. Twenty-four hours before repeating Holter monitoring, all patients underwent an exercise stress test according to a standardized protocol.

Control group. Fifteen age-matched healthy subjects (13 men, 2 women; mean 58 years, range 49 to 63), selected from among potential candidates admitted to the hospital for evaluation of chest pain, formed the control group (Group C). A history, physical examination, chest radiography, echocardiography, exercise electrocardiography and supine and standing blood pressures were recorded for each potential candidate. If any evidence of disease was found the subject was excluded. In these subjects 24-h Holter monitoring was performed twice at 2-week intervals to check for spontaneous heart period variability variations. Recordings were obtained first in hospital and second in the outpatient setting, as in the study patients.

Drug administration. At the time of first evaluation all patients were treated with a calcium channel blocking agent, usually diltiazem, 60 mg three times a day, and with long-acting nitrates, aspirin or calciheparin. It was recommended that patients continue this treatment after discharge.

Echocardiography. Patients were studied in the left lateral decubitus position using parasternal, apical and subcostal views. Wall motion was evaluated in 11 segments of a left ventricular model derived from that proposed by Edwards et al. (17) and modified to consider the apex as a single segment. Studies were considered adequate for analysis only when each of these 11 segments was included in at least one view. Wall motion in each segment was graded on a scale of 1 to 4 (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic) (18), and a summed segment score was calculated by summing the score for each segment.

The examinations, stored on videotape, were reviewed and analyzed by two observers unaware of each other's interpretations and without advance knowledge of the patient's clinical data. Concordance of analysis was achieved in 94% of cases; in the remaining 6% the studies were reviewed and agreement obtained.

Processing 24-h Holter recordings. All 24-h Holter recordings were analyzed at the National Research Council Laboratory of Cybernetics using a homemade analyzer built around a Motorola 68030 50-MHz microprocessor. The two electrocardiographic (ECG) analog channels, read by means of a modified TEAC-TASCAM 234 Syncaset tape deck at 60 times the recording speed, was sampled at 10 kHz. In addition to evaluation of the usual ECG variables, including identification of QRS widths and shapes and RR interval abnormalities, the sequences of all RR intervals were stored, and each RR interval was labeled with a code number identifying its normality or class of abnormality. Patients with persistent rhythm anomalies and tapes with excessive artifacts were excluded. Data losses due to artifacts did not exceed one-third of the time during both daytime (7:30 AM to 9:30 PM) and nighttime (12:00 PM to 5:00 AM). The sequence of normal RR intervals (NN), after exclusion of each abnormal interval and of the two before and after it, used only for timekeeping purposes, was analyzed to compute frequency domain measures of heart period variability (19).

Frequency domain measures of heart period variability. Spectral analysis of RR intervals makes it possible to study their frequency-specific oscillations. Thus, in contrast to time domain analysis, not only the amount of variability but also the oscillation frequency can be obtained. Therefore, in this study we considered frequency domain variables because they comprise a mutually exclusive, all-inclusive categorization of heart period variability.

The heart period power spectrum was computed by means of the fast Fourier transform algorithm, averaging 42 spectra, for a total of 17 h, 30 min. The problem of obtaining an RR interval function of time from the sequence of RR intervals (20,21) has been dealt with as follows: from the sequence of NN values, the other sequence of $\Delta NN_i = NN_{i+1} - NN_i = f(NN_i, NN_{i+1})$ was evaluated, and from the latter the temporal sequence $\Delta NN = f(i)$, $i = 100, 200, 300, \ldots$ ms was computed by linear interpolation with a time step of 100 ms (22,23). Fifteen consecutive ΔNNi values were averaged to obtain samples at the required sampling frequency. The final average spectrum provided total power and average power per band (in ms^2).

The frequency bands explored were 1) *total power* (the energy in the heart period power spectrum between 0.00066 and 0.40 Hz); 2) *ultra low frequency* (the energy in the heart period power spectrum between 0.00066 and 0.0033 Hz); 3) *very low frequency* (the energy in the heart period power spectrum between 0.0033 and 0.04 Hz); 4) *low frequency* (the energy in the heart period power spectrum between 0.04 and 0.15 Hz); and 5) *high frequency* (the energy in the heart period power spectrum between 0.15 and 0.40 Hz).

Because the range of frequencies was very wide, an epoch of 1,500 s and a sampling period of 1.46 s were chosen to cover the entire range, with a sufficient number of frequency samples in each band, as follows: ultra low frequency, 5 samples; very low frequency, 55 samples; low frequency, 165 samples; and high frequency, 227 samples.

Angiography and coronary angioplasty. Severity of all coronary lesions was determined by visual assessment with the consensus of two experienced angiographers. Left ventricular ejection fraction was calculated in the 30° right anterior oblique projection using the area-length method (24). All vessels subjected to coronary angioplasty had

>70% lumen diameter narrowing; coronary angioplasty was performed with standard techniques and equipment (25). Generally, three to five inflations of 60 to 90 s in duration were performed until improvement in the lesion was noted on subsequent angiography. Successful coronary angioplasty was defined as reduction in lesion severity to a lumen diameter <50% compared with the adjacent normal vessel.

Exercise test. A symptom-limited exercise stress test was performed utilizing a bicycle ergometer with stepwise increments of 25 W every 2 min, after an initial 2 min at zero load. Twelve-lead ECGs were recorded at rest, at the end of each 2-min stage of exercise, at maximal exercise and at 1,3,5,7 and 10 min of recovery. Leads V_4, V_5 and V_6 were displayed continuously on a three-channel oscilloscopic monitor. Arterial blood pressure was measured by cuff sphygmomanometer every minute during exercise and the recovery phase.

Exercise test results were classified as follows: 1) *positive* (≥1 mm horizontal or downward ST segment depression or typical angina, or both, appearing during or immediately after exercise); 2) *nondiagnostic* (no significant ST segment changes in patients who failed to achieve ≥85% of the theoretic maximal heart rate for age); or 3) *negative* (no angina or significant ST segment changes and >85% of maximal heart rate achieved).

Statistical analysis. Categoric variables were expressed as percent and were compared using the chi-square test. Continuous data were expressed as mean value ± SD and were analyzed using one-way analysis of variance; if a significant ($p < 0.05$) F test was found, the Student t test for unpaired observation with the Bonferroni correction was used for multiple comparison; a paired t test was performed to evaluate data obtained in the same group.

Because the distribution of the frequency domain measures of heart period variability are extremely skewed, the log transformation (ln) of each measure (which produces nearly normal distributions) was applied before statistical analysis was performed. Statistical significance was defined as $p < 0.05$.

Results

Three patients from Group A and five from Group B were excluded because at follow-up they performed a nondiagnostic or positive stress test or had recurrence of their symptoms. Thus, the final study group consisted of 15 control subjects and 12 patients with normal and 20 patients with abnormal baseline segmental left ventricular wall motion.

Baseline characteristics. Age and gender were comparable among the three groups. History of previous myocardial infarction was present in 33% of patients in Group A (Table 1) and in 60% of patients in Group B (Table 2). Left ventricular ejection fraction was lower in Group B (45.0% ± 5.6%) than in Group A (53.7% ± 4.3%, $p < 0.01$) and Group C (56.8% ± 4.7%, $p < 0.01$).

With regard to heart period variability measurements (logarithmic units), low frequency power was lower in Group B (6.14 ± 0.23) than in Group A (6.34 ± 0.26, $p < 0.05$) and Group C (6.35 ± 0.31, $p < 0.05$). High frequency power was also lower in Group B (5.43 ± 0.32) than in Group A (5.69 ± 0.30, $p < 0.05$) and Group C (5.70 ± 0.38, $p < 0.05$) (Table 3). No difference was detectable in low and high frequency power between Groups A and C. Furthermore, no difference was detectable in the three groups with respect to average NN intervals and ultra low and very low frequency and total power. In Group C no change was detectable in the heart period power spectrum between the two studies.

Table 3. Heart Period Variability in Patients With Normal (Group A) or Abnormal (Group B) Segmental Left Ventricular Wall Motion Before and After Coronary Angioplasty and in Control Subjects (Group C)

	Group A		
	Before PTCA	After PTCA	p Value
Average NN interval (ms)	882 ± 96	875 ± 84	NS
ln total power	9.52 ± 0.37	9.55 ± 0.31	NS
ln ULF power	9.32 ± 0.42	9.35 ± 0.37	NS
ln VLF power	7.27 ± 0.31	7.30 ± 0.29	NS
ln LF power	6.34 ± 0.26	6.29 ± 0.27	NS
ln HF power	5.69 ± 0.30	5.58 ± 0.46	NS
	Group B		
	Before PTCA	After PTCA	p Value
Average NN interval (ms)	884 ± 97	873 ± 98	NS
ln total power	9.50 ± 0.35	9.55 ± 0.34	NS
ln ULF power	9.31 ± 0.41	9.34 ± 0.41	NS
ln VLF power	7.24 ± 0.23	7.28 ± 0.31	NS
ln LF power	6.14 ± 0.23*	6.35 ± 0.34	< 0.01
ln HF power	5.43 ± 0.32*	5.68 ± 0.52	< 0.01
	Group C		
	1st Recording	2nd Recording	p Value
Average NN interval (ms)	887 ± 71	885 ± 76	NS
ln total power	9.54 ± 0.21	9.53 ± 0.20	NS
ln ULF power	9.34 ± 0.26	9.33 ± 0.25	NS
ln VLF power	7.33 ± 0.23	7.34 ± 0.18	NS
ln LF power	6.35 ± 0.31	6.35 ± 0.32	NS
ln HF power	5.70 ± 0.38	5.70 ± 0.38	NS

*$p < 0.05$ comparing Group B with Groups A and C. Data presented are mean value ± SD. HF = high frequency; LF = low frequency; ln = natural logarithm; NN = normal RR interval; PTCA = percutaneous transluminal coronary angioplasty; ULF = ultra low frequency; VLF = very low frequency.

Effects of successful coronary angioplasty. After coronary angioplasty no patient in Group A showed segmental left ventricular abnormalities, and no change was observed in the frequency domain measures of heart period variability (Table 3). In Group B the summed segment score improved from 17.1 ± 3.6 to 12.8 ± 2.0 ($p < 0.01$). Mean low and high frequency power increased from 6.14 ± 0.23 to 6.35 ± 0.34 ($p < 0.01$) and from 5.43 ± 0.32 to 5.68 ± 0.52 ($p < 0.01$),

respectively. No difference was detectable in mean NN interval and in ultra low and very low frequency and total power (Table 3). Furthermore, low and high frequency power, lower at baseline in Group B, were comparable in the three groups after successful coronary angioplasty (Table 3).

Correlation of heart period variability with summed score and ejection fraction. No correlation was found between any measure of heart period variability, summed segment score and angiographic ejection fraction.

Discussion

The results of this study demonstrate that in patients with one-vessel coronary artery disease low and high frequency components of the heart period power spectrum are reduced only when segmental left ventricular dysfunction is detectable. In fact, patients with one-vessel coronary artery disease without regional wall motion abnormalities show heart period variability measures comparable with those obtained in control subjects. Moreover, the recovery in segmental dysfunction by coronary angioplasty is associated with an improvement in heart period variability.

Control group. The high and low frequency values that we observed in the control group are lower than those reported by Kaufman et al. (26) and Goldsmith et al. (27). However, the mean ages of normal subjects in these two studies were 32 and 29 years, respectively, whereas we selected age-matched control subjects whose mean age was 58 years. It is well known that heart period variability is reduced with age (28). Accordingly, Dougherty and Burr (29) studied five normal subjects with a mean age of 58 years and observed heart period variability values similar to those we found.

Heart period variability and extent of coronary artery disease. The relation between autonomic cardiac function and angiographic features of coronary artery disease is controversial. Rich et al. (13) found no correlation between heart period variability and number of diseased vessels. More recently Hayano et al. (14) reported that coronary artery disease is associated with vagal impairment in autonomic cardiac function that correlates with the extent of coronary atherosclerosis and, to a lesser degree, with the severity of coronary stenosis. The results of our study demonstrate that in patients with one-vessel coronary artery disease, heart period variability measures are reduced only when regional left ventricular dysfunction is detectable. In fact, heart period variability values were comparable between control subjects and patients with one-vessel coronary artery disease but without left ventricular dysfunction.

We cannot evaluate whether the number of diseased vessels independently influences heart period variability. In fact, to clarify the role of reversible mechanical dysfunction at comparable angiographic severity, we enrolled only patients with one-vessel coronary artery disease.

Segmental left ventricular dysfunction and heart period variability. The existence of reversible depression of contractility in patients with coronary artery disease has been well documented (30–33), and two-dimensional echocardiography is a noninvasive technique capable of visualizing the improvement in segmental wall motion abnormalities after successful coronary angioplasty (25).

It has been demonstrated that an alteration in cardiac geometry secondary to the presence of a necrotic or noncontracting segment may increase the discharge of sympathetic afferent fibers by mechanical distortion of their sensory endings (34). Such a sympathetic excitation interferes with tonic activity of vagal fibers directed to the sinus node (35,36). The lower values of low and high frequency power observed at baseline in Group B compared with Group A and C patients, and the lack of differences between the latter two groups, support the hypothesis that regional left ventricular dysfunction is involved in determining the impairment in autonomic cardiac control.

Successful coronary angioplasty and heart period variability. After coronary angioplasty, low and high frequency power increased in Group B and were comparable to that obtained in Groups A and C. We hypothesized that the improvement in left ventricular dysfunction after coronary angioplasty could have reduced the discharge of the sympathetic afferent fibers, restoring sympathovagal balance.

High frequency power represents a measure of the modulation of vagal tone by respiratory frequency and depth (37,38). Thus the increase in high frequency power after coronary angioplasty reflects the recovery of parasympathetic nervous activity.

Low frequency power, measured under strictly controlled circumstances using the autoregressive analysis, has been considered an indicator of sympathetic nervous system activity (6,38). However, during 24-h recording it reflects predominantly parasympathetic activity (39–41). Therefore, the increase in low frequency power we observed after coronary angioplasty also indicates a recovery of parasympathetic activity. Most likely, regional left ventricular dysfunction may increase afferent sympathetic activity from the heart, which in turn inhibits efferent vagal nerve activity other than induces an increase in efferent sympathetic activity. Thus, after coronary angioplasty the improvement in regional left ventricular dysfunction could have reduced afferent sympathetic activity, which results in an improvement in Holter measures of vagal activity. The existence in the left ventricle of receptors subserved by vagal afferent fibers must also be considered; the activation of these receptors elicits cardioinhibitory vasodepressor and sympathoinhibitory responses (42). In particular, the discharge pattern of ventricular receptors with unmyelinated afferents is influenced by increases in preload and afterload and by a change in cardiac contractility (43). Therefore, the recovery of regional left ventricular function may conceivably increase the firing of these vagal afferent fibers and, as a

consequence, increase the activity of vagal fibers directed to the sinus node.

The lower values of low and high frequency power observed at baseline in Group B also could be the consequence of reduced coronary flow. The lack of variation in heart period variability after coronary angioplasty in patients with normal baseline echocardiographic wall motion did not support this hypothesis.

Ultra low and very low frequency power. The source of ultra low and very low frequency power is uncertain (44,45). The lack of modification of these components of the power spectrum in our patients confirms that neural cardiac afferent activity does not contribute to their origin.

Drug therapy. No patient in this study was receiving beta-adrenergic blocker agents or angiotensin-converting enzyme inhibitors, drugs with significant effects on heart period variability (40,45). With respect to diltiazem, Bekheit et al. (46) demonstrated that in postinfarction patients this drug reduces energy in the low frequency range in the tilt position but seems to have no effect on heart period variability when assessed by 24-h Holter monitoring (40). However, it must be noted that medical treatment was the same before and after coronary angioplasty.

Study limitations. The lower values of the low and high frequency power, observed at baseline in Group B also may be due to the higher number of patients with previous myocardial infarction in this group. In fact, in Group A only 4 of 12 patients had a previous myocardial infarction; of these none was anterior. This baseline difference of infarct location may be relevant because earlier data have demonstrated that anterior wall myocardial infarction results in a more profound reduction in heart period variability than inferior infarct location (47). However, it must be borne in mind that after coronary angioplasty the power spectrum was comparable in the two groups, despite the differences in infarct location.

Ejection fraction was lower in Group B patients. In agreement with earlier reports (13,15), we found no correlation between frequency domain measures and ejection fraction. Nevertheless, this variable could have influenced the results we observed. In addition, assessment of angiographic ejection fraction after coronary angioplasty could be useful in clarifying the relative roles of global and regional left ventricular dysfunction.

Finally, to better clarify the mechanisms underlying recovery of heart period variability after coronary angioplasty it would be useful to evaluate a group of patients with achieved patency of coronary vessel without improvement in wall motion. However, in our study patients the success of coronary angioplasty was always followed by recovery of wall motion.

Conclusions. The results of this study offer new insights into the mechanism underlying the reduction of heart period variability in patients with coronary artery disease and demonstrate that regional left ventricular dysfunction is involved in determining sympathovagal imbalance in these patients. The recovery of segmental dysfunction after coronary angioplasty is associated with an improvement in autonomic cardiac control of heart rate.

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